CELLTECH

May 6, 2004

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Room 1061 (HFA-305)
Rockville, MD 20852

Re: NDA 21-259 Metadate® CD (methylphenidate HCl, USP)
Extended-Release Capsules - Citizen Petition

Dear Sir/Madam:

Celltech Pharmaceuticals, Inc. submits this petition pursuant to section 505 of the Federal Food, Drug and Cosmetic Act and 21 C.F.R. § 10.30. Celltech requests that the Commissioner of Food and Drugs require an additional bioequivalence test beyond conventional bioequivalence metrics to assure that generic versions of its product Metadate® CD, extended release methylphenidate HCl, are not inappropriately characterized as bioequivalent to the reference product based on insufficiently descriptive pharmacokinetic criteria. Applying this additional bioequivalence test will provide greater assurance that these drugs are safely and effectively used in the clinical management of patients, primarily children. This petition is similar to, and relies upon, the analyses and data set forth in McNeil Consumer & Specialty Pharmaceuticals' Citizen Petition of March 19, 2004, regarding McNeil's product, Concerta® (2004P-0139). Celltech incorporates by reference the applicable arguments, analyses, and data in McNeil's petition. The sole reason Celltech is submitting its own petition is to ensure that generic formulations of its product, Metadate® CD, are subject to the same bioequivalence standards as McNeil's Concerta®.

A. Action Requested

Conventional bioequivalence metrics, while useful in determining bioequivalence for many drug products, are inadequate measures of bioequivalence for certain extended release methylphenidate HCl products that were formulated to produce multiple peaks of methylphenidate in plasma concentration over time. These formulation differences have been shown to result in measurable differences in the magnitude of early clinical effect and the duration of clinical effect in patients with attention deficit hyperactivity disorder (ADHD). Additionally, the extended release technologies vary from product to product, affecting patients taking different methylphenidate drugs differently.

This petition requests that FDA require an additional bioequivalence test, namely area under the curve to the population median Tmax of the reference formulation (AUCpR), in addition to area under the curve to the last measured time point (AUC_{0-t}), or extrapolated to infinity ($AUC_{0-infin}$) and maximum plasma concentration (C_{max}) to more accurately assess therapeutic equivalence to

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2004P-0225

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Metadate® CD when reviewing abbreviated new drug applications (ANDAs) for which Metadate® CD is the reference listed product.

B. Statement Of Grounds

Methylphenidate has been used effectively in the treatment and management of ADHD in children. Eight to ten percent of all school-age children are affected with ADHD, making it the most commonly diagnosed childhood behavioral disorder.[1] Symptoms include hyperactivity, impulsivity, and inattention, leaving untreated children with cognitive processing difficulties that affect both social behavior and academic performance. Methylphenidate, a mild central nervous system stimulant, has been proven to positively affect cognitive processing, academic performance, social behavior, and aggression.

Because ADHD symptoms manifest over the course of a day, it is clinically important for children to have these symptoms managed predictably. Effective plasma and cerebrospinal fluid concentrations of methylphenidate during school hours contribute to optimum levels of cognitive functioning, peer and teacher interaction and academic performance. Variances in methylphenidate clinical effectiveness over time may significantly affect a child's ability to function well during critical periods of the day.

Methylphenidate is a short-acting stimulant with a short half-life; typically, its use requires multiple doses to maintain its treatment effects during the course of a day. Extended release formulations that allow for once daily dosing provide for greater patient compliance, especially in a patient population consisting largely of children.

Not all extended release formulations of methylphenidate HCl are alike, however, and extended release methylphenidate products with similar total methylphenidate content may have dramatically different pharmacokinetic profiles. Different technologies for extending drug release and different proportions of immediate release methylphenidate result in differences affecting the drug's early magnitude of effect, degree of acute tolerance, and duration of effect. For example, Gonzalez, et al[2] studied the effects of two extended release methylphenidate HCl products, Celltech's Metadate® CD capsule and Concerta® tablets, on plasma concentration rate and extent of absorption in a crossover design. While both drugs were found to meet conventional pharmacokinetic criteria for bioequivalence , the study found that greater exposure and higher concentrations of methylphenidate were produced using Metadate ®CD in the first 6 hours after dosing, "a period that corresponds to an important part of the school day."[3] The

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1 American Academy of Pediatrics Committee on Quality Improvement and Subcommittee on Attention-Deficit/Hyperactivity Disorder. Diagnosis and Evaluation of the Child with Attention Deficit/Hyperactivity Disorder. Pediatrics. 2000; 105: 1158-1170.

2 Gonzalez MA, Pentikis HS, Anderl N, et al. Methylphenidate bioavailability from two extended-release formulations. Inter J Clin Pharm Ther 2002:40:175-184.

3 Id. at 175.

authors opined that higher methylphenidate plasma concentration levels early on after dosing, "may be beneficial to children and adolescents who require heightened mental alertness during the early part of the school day."[4]

Conventional bioequivalence determinations are based on 3 measures: $AUC_{0\text{-}t}$, $AUC_{0\text{-}infin}$, and C_{max}. $AUC_{0\text{-}t}$ is the area under the concentration/time curve from 0 to a definite time (t). $AUC_{0\text{-}infin}$ is determined as the summation of area computed to the last observation and extrapolated area to infinity. C_{max} is the observed maximum plasma concentration after drug administration. For many drugs, the extrapolated area under the curve $AUC_{0\text{-}infin}$ represents a significant amount of the total area represented by $AUC_{0\text{-}infin}$. Because methylphenidate products have such a short half life, plasma concentrations are close to the limit of detection by 24 hours. This results in $AUC_{0\text{-}t}$ at 24 hours and $AUC_{0\text{-}infin}$ values that are similar. Because these values are so similar, this petition will address only $AUC_{0\text{-}infin}$, and C_{max} comparisons.

Methylphenidate drugs deemed bioequivalent based on $AUC_{0\text{-}infin}$, and C_{max} measurements, may not be clinically equivalent. Because certain extended release methylphenidate drugs have multiple peaks in plasma concentration, C_{max} would provide a poor estimate of the rate of drug absorption.[5] Therefore, using C_{max} in conjunction with $AUC_{0\text{-}infin}$ may result in a determination that two extended release methylphenidate formulations are bioequivalent, when they are not in fact clinically equivalent.

This result was demonstrated in the Gonzalez study cited above. The Gonzalez study compared single doses of Metadate® CD and Concerta® in healthy, fasting volunteers. Plasma concentrations of methylphenidate were significantly higher for Metadate CD than for Concerta® for up to 6 hours after the initial dose, however, plasma concentrations were significantly higher for Concerta® at 8, 10, and 12 hours after dosing. Despite these striking differences, when compared for $AUC_{0\text{-}infin}$ and C_{max} , the drugs met current FDA criteria for bioequivalence. Gonzalez, however, also used an additional measure, calculating partial areas under the curve (reported in the McNeil citizen petition as AUCpR[6], area under the curve to the population median T_{max} of the reference formulation). When applying the additional measurement of AUCpR, however, a higher partial area under the plasma concentration curve was shown for Metadate® CD suggesting that, based on this measure, the two drugs were likely to be therapeutically inequivalent.

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4 Id. at 184 (There's different numbering on the reprint than the published article – but the quote is on the last page of text.)

5 Chen ML, Lesko L, Williams R. Measures of exposure versus measures of rate and extent of absorption. Clin Pharmacokinet. 2001; 40:565-572.

6 The Gonzalez study did not report AUCpR, but partial areas up to four, six and eight hours. AUC4th, used by McNeil as AUCpR, most closely approximates AUCpR as the mean Tmax for Metadate CD is about 4 hours.

The prediction of therapeutic inequivalence for the Metadate® CD and Concerta® dose-pairs compared in Gonzalez was confirmed in Swanson, et al.[7] Swanson studied the behavior and attention of 184 ADHD children over a 12 hour day using a randomized, double-blind, three treatment crossover design. Clinically and statistically significant differences between formulations were observed for validated measures of behavior and academic productivity. The direction of significant differences at any assessment time was found to correlate closely with the predicted differences in plasma methylphenidate concentration at that time.

FDA's previously stated concerns over partial area metrics should not apply to bioequivalence determinations of certain extended release methylphenidate HCl products that have been designed to produce multiple peaks of methylphenidate in plasma concentration FDA has previously expressed concern that partial area metrics are highly variable and thus, unreliable as a measure of bioequivalence (citing variability of >30%). However, the data presented to FDA recently in the March 19, 2004 McNeil Citizen Petition[8] regarding Concerta® demonstrated that when AUCpR was applied, there was, in fact low intra-subject variability (8.3 - 18.5%). These data are significantly lower than FDA's stated estimates. McNeil correctly points to the unique properties of methylphenidate that make AUCpR an appropriate supplemental metric for determining bioequivalence in these drugs. Additionally, McNeil noted that the examples cited in FDA's correspondence did not assess the relationship between AUCpR and clinical effects. Therefore, FDA's previous stated concerns should not prevent the use of this metric as a supplement to average bioequivalence measures when analyzing certain extended release methylphenidate products.

AUCpR is a measurement sensitive to differences in absorption profiles and clinical effects among extended-release methylphenidate products. The data described in the Gonzalez study demonstrates low intra-subject variability and reinforces the use of AUCpR as an additional bioequivalence metric to ensure therapeutic equivalence. FDA should require that AUCpR be an additional bioequivalence metric when analyzing whether a generic version of extended release methylphenidate HCl is therapeutically equivalent to the innovator product. The failure to include this measurement in analyzing an ANDA may result in approval of a therapeutically inequivalent drug that may adversely affect children, the primary patient population.

C. Environmental Impact

The action requested is subject to a categorical exemption from environmental assessment under 21 C.F.R. §§ 25.22 and 25.31.

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7 Swanson JM, Wigal SB, Wigal T, et al., A Comparison of Once-Daily Extended-Release Methylphenidate Formulations in Children With Attention-Deficit/ Hyperactivity Disorder in the Laboratory School, Pediatrics March 2004: 113: No. 3 206-216.

8 McNeil Consumer & Specialty Pharmaceuticals Citizen Petition, March 19, 2004. 2004P-0139

D. Economic Impact

Pursuant to 21 C.F.R. § 10.30, Celltech will provide data concerning the economic impact of the relief requested should such information be requested by FDA.

E. Certification

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner, which are unfavorable to the petitioner.

Sincerely,

Norman D. LaFrance, MD, FACP, FACNP
Senior Vice President,
Medical & Regulatory Affairs